REMARKS

Claims 1-3, 5-7 and 9-11 are all the claims pending in the application. Claim 1 has been amended, and support for the amendments can be found throughout the specification and originally filed claims. Specifically, the support for the amendment can be found in the original claim 1 and [0041]. *U.S. Publication No. 2007/0116676.* Accordingly, no new matter has been introduced by these amendments to claims.

Claim Rejections under 35 U.S.C. § 103

Claims 1-3, 5, 6 and 9-11 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Goodwin #1 (USP 5,496,722), Goodwin #2 (In Vitro. Cell Dcv. Biol., vol 33, page 358, 1997), Goodwin #3 (In Vitro. Cell Dev. Biol., vol 33, page 366, 1997) and Schwarz et al. (USP 5,026,650) in view of Unsworth et al. (Nature Medicine), Wikipedia, Bock et al. (Tissue Engineering of Cartilage and Bone) and Bartlett (Ovarian Cancer Methods and Protocols).

The Examiner asserts that Goodwin #1 discloses culturing bone marrow mesenchymal cells in a Rotating Wall Vessel (RWV), taught by Schwarz et al. that can control the rotation speed. The Examiner admits that Goodwin #1, however, does not teach the confluent two-dimensional (2D) culture of mesenchymal cells prior to the culture in RWV. Regarding the deficiency of Goodwin #1, the Examiner asserts that Goodwin #2 and #3 in light of Bock and Bartlett disclose the confluent 2D culture of chondrocytes and ovarian tumor cells, respectively, prior to a passage and render such culture of mesenchymal cells obvious.

Applicants have amended claim 1 to clarify the scope of the claim and specify the subculture from confluent 2D culture to 3D culture. *[0041] of U.S. Publication No. 2007/0116676.*

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

In making the rejection, the Examiner asserts that Goodwin #2 and #3 disclose 2D culture prior to 3D culture, and Bock and Bartlett disclose confluent 2D culture prior to a passage. *Office Action of April 28, 2008*, page 6. The Examiner appears to take apart a single element, the

subculture from confluent 2D culture to 3D culture, and separate it into two elements, namely the confluent 2D culture and the priority of the 2D and 3D cultures. However, in the present invention, there is no subculture from the 3D culture to the confluent 2D. Accordingly, the subculture from the confluent 2D cell culture to 3D culture is a single element. *See* U.S. Publication No. 2007/0116676 at [0041]. When read in context, it is apparent that Goodwin #1, #2 and #3, Bock, and Bartlett, alone or in combination, fail to teach this single element. Moreover, neither Schwarz nor Unsworth, cure such deficiency.

To establish *prima facie* obviousness of a claimed invention, all the cited references must recite all the claim limitations. *In re Royka,* 490 F.2d 981, 984 (CCPA 1974). For the reasons previously presented above, Applicants contend that the combination of cited references fails to teach or suggest all the claim limitations of the invention, either explicitly or inherently. In particular, these references do not expressly or inherently teach the subculture from confluent 2D culture to 3D culture. Thus, these references do not support a *prima facie* case of obviousness.

Additionally, Applicants assert that one of ordinary skill in the art would have no reasonable expectation of success in incorporating the confluent 2D culture of chondrocytes or ovarian tumor cells in the culture of mesenchymal cells because it is well-known in the art that the properties of undifferentiated mesenchymal cells are different from those of fully differentiated chondrocytes or ovarian tumor cells. The Examiner states that "[t]his is a simple matter of applying known cell culture technique to expand and produce enough cells for an adequate sized inoculum for an RWV" *Office Action of April 28, 2008*, page 6. Here, the Examiner appears to assert that the reason for the above alteration and/or combination is to increase the number of cells. Goodwin #1, however, states that "[h]uman bone marrow cell production declines over time in monolayer culture," and such low proliferation in the conventional monolayer culture was a motivation to develop Goodwin's 3D culture method in the first place. Col. 4, lines 20-24. Therefore, Goodwin #1 essentially discourages the use of the 2D monolayer culture to expand mesenchymal cells. Moreover, it is well known in the art that chondrocytes dedifferentiate into fibroblastic cells when they are subjected to 2D culture (Holtzer et al., Proc Natl Acad Sci USA. 1960 Dee; 46(12): 1533-42.; attached hereto). Further, since ovarian tumor cells are not normal cells, their properties concerning proliferation and differentiation are different from those of mesenchymal cells. Thus, indeed, there is no reason for

one of ordinary skill in the art to have a reasonable expectation of success in incorporating the confluent 2D culture of chondrocytes or ovarian tumor cells.

Furthermore, Applicants respectfully point out that Applicants are not claiming an expansion or production of mesenchymal cells in any of the pending claims. Rather, Applicants are claiming a differentiation of mesenchymal cells to make cartilage tissue. Therefore, Applicants assert that the Office Action fails to establish a reason as to why one of ordinary skill would pursue the techniques to expand chondrocytes or ovarian tumor cells in the differentiation of mesenchymal cells. As the Supreme Court recently discussed, the "apparent reason to combine the known elements in a fashion claimed by the [claims] at issue ... should be made explicit." *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 slip op. at 14 (U.S. Apr. 30, 2007). Rather than indicating why one of skill in the art would choose to combine the references in a method for cell differentiation, the Examiner is silent.

In this invention, the confluent 2D culture is carried out for the purpose of producing cell matrix and promoting the differentiation of the cells into cartilage rather than increase in cell number. In cartilage tissue, the cells are not so dense that they generally do not contact directly with each other, and they seem to receive signals from matrix around them. By the confluent 2D culture, a sufficient amount of matrix proteins for supporting the cells in the 3D culture is produced such that the cells can efficiently differentiate and produce matrix in the 3D culture. Thus, the purpose of the confluent culture in this invention is completely different from that of cited references.

Moreover, the confluent 2D culture prior to subculturing is out of the common general knowledge in the field of cell culture. A person skilled in the art normally subcultures the cells when the cells grow to 70 to 90% confluency. It is known in the art that, if the cells are cultured to 100% confluency, then the proliferation property of the cells may be affected or the phenotype of the cells may alter due to contact inhibition. Thus, it is atypical to conduct the confluent 2D culture prior to subculturing.

For the reasons set forth above, Applicants assert that there is no apparent reason that would lead one of skill in the art to make the proposed modification.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in the cited references, and thus request withdrawal of the Examiner's rejection.

Claims 1-3, 5-7 and 9-11 are rejected under 35 USC § 103(a) as being unpatentable over Goodwin #1, #2, #3 and Schwarz et al,, and further in view of Yan et al. (US 2002/0168763) and Simpson et al. (US 2002/0090725).

Claim 7 directly depends on claim 1. Therefore, reasons presented above for claim 1 also apply in the present rejection. Namely, it has been shown above that the combination of Goodwin #1, #2, #3 and Schwarz fails to teach or suggest the subculture from confluent 2D culture to 3D culture. Neither Yan nor Simpson cures such deficiency. Applicants respectfully assert therefore that the subject matter of the instant claims is non-obvious over the disclosures of the cited references. Because the cited references do not teach all of the claim limitations, there can be no reasonable expectation of success in combining the cited references to arrive at the claimed invention. Thus, these references do not support a *prima facie* case of obviousness.

For the reasons set forth above, Applicants respectfully maintains that the combination of the cited references, taken alone or in combination, fail to recite and teach all the limitations of the claimed invention. Moreover, Applicants assert not only that one of ordinary skill in the art would have no reasonable expectation of success in combining references, but also that there is no reason for one of skill in the art to make the proposed modification. Accordingly, Applicants assert that the combination of cited references fails to render obvious the claimed invention.

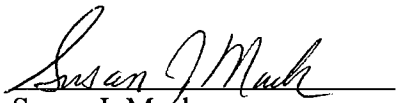
Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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